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REVIEW ARTICLE

Nutritional Interventions in Cancer Prevention

Philip R. Taylor and Peter Greenwald

ABSTRACT

The first generation of phase III nutritional intervention studies to prevent cancer has been completed. Nearly 150,000 total participants were studied in nine different interventions using randomized, double-blind, placebo-controlled designs that tested whether vitamins and/or minerals, given singly or in combination, could prevent total or site-specific cancer. The primary agents tested include beta-carotene, alpha-tocopherol, selenium, and retinol. This review summarizes the findings from the first generation of human experimental studies that tested micronutrients in the prevention of cancer, discusses lessons learned from these studies, identifies the most promising leads, and describes future prospects in nutritional intervention research.

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INTRODUCTION

Since the publication of two reports in the early 1980s,[1,2] there has been intense interest in the role of nutrition in the etiology and prevention of cancer. In the past 25 years, there have been hundreds of observational studies of diet and cancer, and the vast majority show that individuals who consume more fruit and vegetables have lower cancer risk.[3,4] However, eating more fruit and vegetables, like reducing dietary fat, is challenging. As a society and as physicians, we are far more inclined to prescribe than to proscribe. So, while the evidence (and prudence) most clearly supports modification of food patterns in order to lower cancer risk, we remain reductionists, forever seeking out the easiest solution, preferably a magic molecule in a pill. Arguably, the diet and cancer research that has been the most informative these past 25 years in evaluating causal effects has come from studies that have used the experimental design. As the gold standard of clinical research, randomized, placebo-controlled, clinical trials provide the empirical base of knowledge necessary to make prudent recommendations for the health of patients and the public.

Thus, the purpose of this review is to: (1) summarize findings from the first generation of phase III human experimental studies that have tested nutritional strategies in the prevention of cancer; (2) discuss lessons and the most promising leads from the trials completed to date; and (3) describe future prospects in nutritional intervention research. We will limit this review to those trials that were designed to be large enough to have cancer incidence and/or mortality as primary end points.

NUTRITIONAL INTERVENTIONS IN CANCER PREVENTION: THE FIRST GENERATION OF TRIALS

A summary of the major design features of the nine first generation nutritional interventions in cancer prevention that have reported results to date is shown in Table 1, while results from these trials are summarized in Table 2. Below we describe the trials in chronologic order by initial report.

Skin Cancer Prevention Study

The first nutritional cancer prevention trial completed tested beta-carotene in the prevention of recurrent nonmelanoma (ie, basal cell carcinoma [BCC] and squamous

Table 1. Summary of Major Design Elements for the First Generation of Nutritional Interventions in Cancer Prevention

Element	SCPS[5]	NIT Dysplasia Trial[6]	NIT General Population Trial[7]	ATBC[8]*	PHS[9]
			Nutritional Intervention		
Population	1,805 adults, aged < 85 years with prior BCC or SCC (70% male)	3,318 adults, aged 40-69 years with cytologic dysplasia (44% male)	29,594 adults, aged 40-69 years (45% male)	29,133 male smokers, aged 50-69 years (100% male)	22,071 male physicians, aged 40-84 years (100% male)
Design	Two-arm, randomized, double-blind, placebo-controlled	Two-arm, randomized, double-blind, placebo-controlled	1/2 2⁴ fractional factorial, randomized, double-blind, placebo-controlled	2×2 factorial, randomized, double-blind, placebo-controlled	2×2 factorial, randomized, double-blind, placebo-controlled*
Intervention	Beta-carotene	26 vitamins, minerals	4 different combinations of 9 vitamins, minerals	Alpha-tocopherol and/or beta-carotene	Aspirin and/or beta-carotene
Duration of intervention	5 years	6 years	5.25 years	6.1 years	12 years
Primary cancer end point	1st recurrent BCC/SCC	Esophageal/gastric cardia cancer mortality (incidence)	Esophageal/gastric cardia cancer mortality (incidence)	Lung cancer incidence	Total cancer incidence

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cell carcinoma [SCC]) skin cancers.[5] Nonmelanoma skin cancers were selected as the target end point because they are the most common cancers in the United States, as well as a source of substantial morbidity and mortality, and the most consistent laboratory evidence for an anticancer effect of beta-carotene at the time the trial was planned came from experimental studies of skin cancer in animals. This trial randomly assigned 1,805 patients at high risk for recurrence of nonmelanoma skin cancer (they had to have at least one biopsy-proven BCC or SCC) at one of four medical centers (New Hampshire, Minnesota, and northern and southern California) across the United States between 1983 and 1985 to randomly receive either beta-carotene (50 mg/d) or a placebo identical in appearance. The intervention concluded in September 1989 after follow-up of 5 years.

At the end of the trial, the cumulative probability of a new skin cancer was 43% in the beta-carotene group and 41% in the placebo group (a nonsignificant increase of 5% in the beta-carotene group). Likewise, there was no difference in the (first) recurrence of either BCC (334 subjects with a recurrence in the beta-carotene group *v* 317 in the placebo group, a nonsignificant 4% increase) or SCC (73 *v* 59 subjects, a nonsignificant 22% increase). Nor was there an effect of beta-carotene on the total number of recurrent nonmelanoma skin cancers (a nonsignificant 7% increase in the total number in the beta-carotene *v* placebo group). No difference in recurrence rates between supplementation groups was seen in subgroups defined by sex, age, center, number of previous skin cancers, age at first skin cancer, skin type, smoking status, or baseline levels of either plasma beta-carotene or retinol. Although the study was not designed to be large enough to evaluate death as an end point, the 151 deaths recorded were evenly dis-

tributed between treatment arms (79 in beta-carotene group *v* 72 subjects in placebo group). In summary, no effect of beta-carotene, either beneficial or harmful, was observed in this trial.

Nutrition Intervention Trials (NIT)

A cancer mortality atlas published in China in the mid-1970s initially identified Linxian, a rural county in Henan Province in north-central China, as a unique location to study both etiology and potential prevention strategies for cancer of the esophagus.[16] Over 20% of the population in Linxian die from what has traditionally been called "difficulty swallowing disease"; we now know that this includes a combination of esophageal squamous cell carcinoma (ESCC) and gastric cardia cancer (GCC), and that both occur in Linxian at rates higher than anywhere else in the world.[17] Persons with esophageal dysplasia, a premalignant lesion affecting over 20% of adults in this area, are at especially high risk.[18,19] The extraordinary rates of esophageal/gastric cardia cancer, in combination with documented low levels of numerous micronutrients in Linxian and empirical data from the literature that supported the role of deficiencies of these nutrients in esophageal cancer, provided ample rationale to pursue nutritional interventions in this population to prevent cancer.[20] To test whether multiple vitamins and minerals would reduce esophageal/gastric cardia cancer mortality, two different intervention studies were conducted in Linxian.

NIT Dysplasia Trial

A total of 3,318 individuals 40 to 69 years of age from one of three northernmost communes in Linxian, China (where rates were highest in the county) who participated in a population-based esophageal balloon cytology

Table 1. Summary of Major Design Elements for the First Generation of Nutritional Interventions in Cancer Prevention (continued)

Element	Nutritional Intervention			
	CARET[10]	NPC[11,12]†	WHS[13]	SKICAP AK Trial[14]
Population	18,314 adults, aged > 45 years with asbestos and/or smoking exposure (66% male)	1,312 adults, aged 18-80 years with prior BCC or SCC (76% male)	39,876 women, aged ≥ 45 years (0% male)	2,297 adults, aged 21-84 years with ≥ 10 AKs and ≤ 2 prior SCCs or BCCs (70% male)
Design	Two-arm, randomized, double-blind, placebo-controlled	Two-arm, randomized, double-blind, placebo-controlled	2³ factorial, randomized, double-blind, placebo-controlled	Two-arm, randomized, double-blind, placebo-controlled
Intervention	Beta-carotene plus retinol	Selenium	Aspirin, alpha-tocopherol, and/or beta-carotene	Retinol
Duration of intervention	4 years	4.5 years (7.9 years)†	2.1 years	3.8 years
Primary cancer end point	Lung cancer incidence	1st recurrent BCC/SCC	Total cancer incidence	1st recurrent SCC/BCC

Abbreviations: SCPS, Skin Cancer Prevention Study; NIT, Nutrition Intervention Trials; ATBC, Alpha-Tocopherol Beta-Carotene study; PHS, Physicians' Health Study; CARET, Beta-Carotene and Retinol Efficacy Trial; NPC, Nutritional Prevention of Cancer study; WHS, Women's Health Study; SKICAP AK, Retinoid Skin Cancer Prevention Actinic Keratosis Trial; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; AK, actinic keratosis.
*Initial report in 1994 included 876 incident lung cancers (ATBC Study Group[15]); updated report in 1996 included 894 lung cancers (Albanes et al[8]).
†Initial report in 1996 (Clark et al[11]) included only part (4.5 years) of the intervention phase, while an updated report in 2002 (Duffield et al[12]) included the entire (7.9 years) intervention phase of the study.

examination in late 1983 and had a diagnosis of esophageal dysplasia were randomly assigned in the Dysplasia Trial to receive daily supplementation with either 14 vitamins and 12 minerals (daily doses of micronutrients included: beta-carotene, 15 mg; vitamin A, 10,000 U; vitamin E, 60 U; vitamin C, 180 mg; folic acid, 800 μg; vitamin B1, 5 mg; vitamin B2, 5.2 mg; niacinamide, 40 mg; vitamin B6, 6 mg; vitamin B12, 18 μg; vitamin D, 800 U; biotin, 90 μg; pantothenic acid, 20 mg; calcium, 324 mg; phosphorus, 250 mg; iodine, 300 μg; iron, 54 mg; magnesium, 200 mg; copper, 6 mg; manganese, 15 mg; potassium, 15.4 mg; chloride, 14 mg; chromium, 30 μg; molybdenum, 30 μg; selenium, 50 μg; zinc, 45 mg) or placebo for 6 years.[6] Doses of vitamins and minerals were in the range of two to three times the US Recommended Daily Allowances (RDA),[21] and were designed to bring low levels up to normal rather than provide pharmacologic doses.

Of the 324 total deaths during this 6-year trial, 157 occurred in the supplement group versus 167 in the placebo group (7% reduction, $P > .05$). While there were no significant differences between the supplement and placebo groups for site-specific cancer mortality rates, there were suggested benefits for supplementation on total cancer (4% lower than placebo), ESCC (16% lower), and the combined ESCC/GCC end point (8% lower). In contrast, an increase in total stomach cancer mortality was suggested for supplementation (18% higher than placebo, $P > .05$), attributable almost exclusively to differences in gastric noncardia cancer (GNCC; eight cases in supplement group v three in placebo group). Cancer incidence results were similar to mortality results, but the comparison for GNCC was statistically significant (14 cases in supplement group v four in placebo), although this comparison was based on a small number of cases. Overall, sup-

plementation effects were consistent with benefit but were not statistically significant for any of the mortality end points evaluated, and GNCC incidence was increased. Additional intermediate end point studies conducted as part of this trial (ie, examination of the effects of supplementation on premalignant histology, epithelial proliferation, and cytologic abnormalities) all provided varying degrees of evidence for benefit from supplementation.[22-25]

NIT General Population Trial

Also conducted in Linxian, the General Population Trial randomly assigned 29,584 adults aged 40 to 69 years from four northern Linxian communes to 5.25 years of daily supplementation with one or more of four different combinations of vitamins and minerals (or placebo) according to a one half replicate 2^4 (two-by-two-by-two-by-two) fractional factorial design.[7] The four combinations (or factors) tested included: factor A (retinol [5000 U] plus zinc [22.5 mg]); factor B (riboflavin [3.2 mg] plus niacin [40 mg]); factor C (ascorbic acid [120 mg] plus molybdenum [30 μg]); and factor D (beta-carotene [15 mg] plus selenium [50 μg] plus alpha-tocopherol [30 mg]). This design permitted tests of the main effects of each factor (eg, factor A v no factor A, and so on) but, because this was not a full four-factor factorial, interactions could not be evaluated. Dosages for this trial were slightly lower than the Dysplasia Trial (one to two times US RDA), and were also designed as repletion (rather than pharmacologic) doses.

A total of 2,127 deaths, including 792 cancer deaths, were recorded during the General Population Trial. Statistically significant beneficial effects on mortality were found for supplementation with factors A (retinol plus zinc) and D (beta-carotene plus selenium plus alpha-tocopherol). Participants supplemented with factor A had

Table 2. Summary of Results From First Generation of Nutritional Interventions in Cancer Prevention: RRs or CRs for Supplement Versus Placebo Group Comparisons

	Nutritional Intervention				
Element	SCPS[5]	NIT Dysplasia Trial[6]	NIT General Population Trial[7]	ATBC[8]	PHS[9]
Primary cancer end point(s)	BCC+SCC, RR = 1.05; BCC, RR = 1.04; SCC, RR = 1.22	ESCC/GCC mortality, RR = 0.92	ESCC/GCC mortality, RR = 1.04 (A); RR = 0.95 (B); RR = 1.06 (C); RR = 0.90 (D);	Lung incidence, RR = 0.99 (AT); RR = 1.16*(BC)	Total cancer incidence, RR = 0.98
Secondary end points	Total death, CR = 1.10; Number BCC+SCC, RR = 1.07	Total death, RR = 0.93; cancer death, RR = 0.96; ESCC death, RR = 0.84; SC death, RR = 1.18; GCC death, RR = 1.04; GNCC death, RR = 2.68 (incidence RR = 3.54*)	Total death, RR = 0.91* (D); Cancer death, RR = 0.87* (D); ESCC death, RR = 0.96 (D); SC death, RR = 1.03 (A), RR = 0.79* (D); GCC death, RR = 1.22 (A), RR = 0.82 (D); GNCC death, RR = 0.59* (A), RR = 0.72 (D)	Total death, RR = 1.02 (AT); RR = 1.08* (BC); Prostate incidence, RR = 0.68*(AT); RR = 1.23 (BC); Colorectal incidence, RR = 0.78 (AT); RR = 1.05 (BC); Urothelial incidence, RR = 1.1 (AT), RR = 1.0 (BC); Kidney incidence, RR = 1.1 (AT), RR = 0.8 (BC); Stomach incidence, RR = 1.21 (AT), RR = 1.26 (BC)	Total death, CR = 1.01; Cancer death, RR = 1.02; Lung incidence, CR = 0.93; Prostate incidence, CR = 0.99; Colorectal incidence, CR = 0.96; Melanoma incidence, CR = 0.88; Lymphoma incidence, CR = 1.08

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a 41% reduction in GNCC deaths, while factor D resulted in reductions in total mortality of 9%, total cancer mortality of 13%, and stomach cancer (GCC and GNCC combined) mortality of 21%. No significant harmful effects on cause-specific mortality or cancer incidence were observed for any of the four supplementation combinations.

Alpha-Tocopherol, Beta-Carotene (ATBC) Study

Lung cancer causes more deaths than any other cancer worldwide and is a major and increasing public health problem. In the 1980s, male lung cancer rates in Finland were the highest in the world, attributed primarily to smoking. These high rates, coupled with typical Finnish diets, traditionally low in fresh fruit and vegetables, and existing health care and cancer registration systems, suggested that Finland would be an excellent setting for a lung cancer prevention trial. To test whether alpha-tocopherol or beta-carotene supplementation would reduce the incidence of lung and other cancers, 29,133 male smokers 50 to 69 years of age from southeastern Finland were randomly assigned to one of four daily supplementation regimens in a two-by-two factorial design: alpha-tocopherol (50 mg) alone, beta-carotene (20 mg) alone, both alpha-tocopherol plus beta-carotene, or placebo. Intervention continued for 5 to 8 years (median, 6.1 years).[15]

A total of 894 new lung cancer cases were identified for the final report of the ATBC study.[8] Lung cancer incidence was unaffected by alpha-tocopherol (a nonsignificant 1% increase); however, beta-carotene supplementation signifi-

cantly increased incidence rates by 16% (482 new cases in beta-carotene group v 412 in no beta-carotene group). Lung cancer mortality patterns followed incidence for both supplements. Total mortality was also unaffected by alpha-tocopherol (nonsignificant 2% increase), although deaths from hemorrhagic strokes (but not ischemic or total strokes) were significantly elevated by 50%.[15] Supplementation with beta-carotene resulted in a significant 8% increase in total mortality, primarily due to more deaths from lung cancer and ischemic heart disease. Detailed analysis of the beta-carotene–induced lung cancer elevation suggested that this effect was most pronounced in men who smoked heaviest and drank the most.[8]

Numerous secondary cancer end points from the ATBC study have also been reported, most prominently the significant 32% reduction in incident prostate cancer among men supplemented with alpha-tocopherol (99 cases in alpha-tocopherol group v 147 cases in no alpha-tocopherol group).[26] Prostate cancer incidence was 23% higher in beta-carotene recipients, although not significantly so. Malignancies at other anatomic sites have also been reported, and among those with at least 100 events, cancers of the colorectum (n = 135),[27] urethelium (bladder, ureter, and renal pelvis, n = 169),[28] kidney (n = 102),[28] and stomach (n = 126)[29] showed no significant effects of either alpha-tocopherol or beta-carotene supplementation, although several suggestive effects were observed (eg, reduced risk of colorectal cancer for alpha-tocopherol, increased risk of intestinal-type stomach cancer for beta-carotene).

Table 2. Summary of Results From First Generation of Nutritional Interventions in Cancer Prevention: RRs or CRs for Supplement Versus Placebo Group Comparisons (continued)

Element	Nutritional Intervention			
	CARET[10]	NPC[11,12]	WHS[13]	SKICAP AK Trial[14]
Primary cancer end point(s)	Lung incidence, RR = 1.28*	BCC+SCC, RR = 1.17*; BCC, RR = 1.09; SCC, RR = 1.25*	Total cancer incidence, RR = 1.03	SCC, RR = 0.74*; BCC, RR = 1.06
Secondary end points	Total death, RR = 1.17*	Total death, RR = 0.79; Cancer death, RR = 0.59*; Total cancer incidence, RR = 0.75*; Lung incidence, RR = 0.74; Prostate incidence, RR = 0.48*; Colorectal incidence, RR = 0.46	Total death, CR = 1.11; Breast incidence, CR = 1.01	Total death, RR = 1.00 (on medication), RR = 1.08 (full 61 months of observation)

Abbreviations: RR, relative risk; CR, case ratio; SCPS, Skin Cancer Prevention Study; NIT, Nutrition Intervention Trials; ATBC, Alpha-Tocopherol Beta-Carotene study; PHS, Physicians' Health Study; CARET, Beta-Carotene and Retinol Efficacy Trial; NPC, Nutritional Prevention of Cancer study; WHS, Women's Health Study; SKICAP AK, Retinoid Skin Cancer Prevention Actinic Keratosis Trial; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; GCC, gastric cardia cancer; AT, alpha-tocopherol; BC, beta-carotene; A, Factor A (retinol + zinc); B, Factor B (riboflavin + niacin); C, Factor C (ascorbic acid + molybdenum); D, Factor D (beta-carotene + selenium + alpha-tocopherol); SC, stomach cancer (GCC + GNCC); GNCC, gastric noncardia cancer.
*P value is statistically significant (P < .05).

Physicians' Health Study (PHS)

To test potential effects of aspirin and beta-carotene on both cardiovascular disease and cancer, the PHS recruited 22,071 male physicians in the United States in 1982 who were 40 to 84 years of age and randomly assigned them using a two-by-two factorial design to one of four groups: aspirin alone (325 mg on alternate days); beta-carotene alone (50 mg on alternate days); both aspirin plus beta-carotene; or placebos. The randomized aspirin component was terminated early (in January 1988) due to a significant 44% reduction in risk of first myocardial infarct in the aspirin group,[30] while the randomized beta-carotene component continued until the end of 1995.

The 2,566 new cancers (excluding nonmelanoma skin cancers) identified during the 12-year trial were essentially evenly distributed between the beta-carotene and placebo groups (a nonsignificant 2% lower rate was seen in the beta-carotene group), as were all important cardiovascular events (no difference by beta-carotene group status based on 1,939 total end points) and total mortality (a nonsignificant 2% increase in the beta-carotene group based on 1,947 total deaths).[9]

Although lung cancer was relatively uncommon in this population, in which only 11% of participants were current smokers, the 170 new lung cancers diagnosed were distributed evenly between the beta-carotene and no beta-carotene groups (82 v 88 cases, respectively). Event rates did not differ by supplementation status when subgroups based on smoking status were examined (ie, nonsmokers, former smokers, current smokers).

While not part of the primary study hypothesis, there were over 100 new events for five other individual cancer sites. Beta-carotene supplementation did not affect incidence of the four most frequent of these cancers (prostate,

520 in beta-carotene group v 527 in placebo group; colorectal, 167 v 174; melanoma, 64 v 73; and lymphoma, 86 v 80), but the number of cases of bladder cancer in the beta-carotene group appeared to be elevated (62 v 41).

Beta-Carotene and Retinol Efficacy Trial (CARET)

The CARET was initiated to address the enormous and increasing burden of lung cancer. Started in 1985 as two pilot studies, subsequently expanded to other centers in 1988 and again in 1991, CARET was designed to test whether the daily beta-carotene (30 mg) plus retinol (25,000 U) supplementation could prevent new lung cancers in persons at high risk.[10] Subjects were recruited and randomly assigned at six study centers from two risk groups: men over 45 years of age with occupational asbestos exposure (n = 4,060), and men or women 50 to 69 years of age who were heavy smokers (ie, at least a 20 pack-year history of cigarette smoking, either current smokers or recent quitters; n = 14,254). The overall trial population then consisted of 18,314 individuals, including 34% females. Intervention was terminated early (December 1995) after an average follow-up time of 4 years.

A total of 388 new lung cancers were diagnosed and 974 deaths occurred during the intervention phase of the CARET study. Compared to placebo, the supplemented group had significantly increased rates of both lung cancer (28% increased) and total mortality (17% increased).

Detailed analyses by subgroups suggested that the increased risk attributed to beta-carotene supplementation was most pronounced in current (as opposed to former) smokers and in participants with the highest alcohol intake.[31] Three other anatomic sites recorded at least 100 malignancies, but none were affected by supplementation: prostate cancer (n = 300 total cases, nonsignificant 1%

increase in beta-carotene group); breast cancer (n = 124, nonsignificant 22% decrease); and colorectal cancer (n = 106, nonsignificant 2% increase).

Nutritional Prevention of Cancer (NPC) Study

The purpose of this study was to determine if supplementation with selenium would decrease the incidence of BCC and SCC of the skin. To test this hypothesis, 1,312 patients aged 18 to 80 years with a history of BCC or SCC were randomly assigned at seven dermatology clinics in the eastern United States between 1983 and 1991 to receive selenium (200 μg daily) or placebo for an average of 4.5 years.[11]

Although the intervention did not end until 1996, the initial report of results from the NPC study included events only through 1993. A total of 727 BCCs and 408 SCCs were included in this analysis, which found nonsignificant increases in both types of skin cancer in the selenium group. Secondary end points reported were based on more modest numbers and included a nonsignificant reduction of total mortality (17%) and significant reductions in total cancer mortality (50%), total cancer incidence (47%), lung cancer incidence (46%), prostate cancer incidence (63%), and colorectal cancer incidence (58%) in the selenium group.[32]

Recent publications of analyses from the entire study period add 3 more years of intervention (average follow-up is now 7.9 years) and show less favorable results than those from the initial report. Total cancer mortality (reduced 41%), total cancer incidence (reduced 25%), and prostate cancer incidence (reduced 52%) still show significant reductions in the selenium group, albeit less than before.[12] However, decreases in lung cancer (26%) and colorectal cancer (54%) incidences are no longer statistically distinguishable from placebo, and the increase in new SCCs in the selenium group noted in the initial report is now a significant finding (25%).[12,33,34]

Woman's Health Study (WHS)

The WHS was designed to test the effects of aspirin, vitamin E, and/or beta-carotene on both cardiovascular disease and cancer (the primary end point was all invasive cancers exclusive of nonmelanoma skin cancers). A total of 39,876 healthy women aged 45 years or older were randomly assigned to this intervention which used a 2^3 (two-by-two-by-two) factorial design to test three factors separately and in combination: aspirin (100 mg every other day), vitamin E (600 mg every other day), and beta-carotene (50 mg every other day).[13] Randomization began in 1993, but the beta-carotene component of the trial was stopped in early 1996 following 2.1 years of intervention after results from the ATBC, PHS, and CARET studies were all known, and concern for the potential harmful effects of beta-carotene was high. The aspirin and vitamin E components of the trial are still ongoing.

After 4.1 years of observation (2.1 years of intervention plus another 2 years of follow-up), 747 confirmed cases of invasive cancer were evenly distributed by beta-carotene supplement status (nonsignificant 3% increase in beta-carotene group). Similarly, breast cancer, the only individual site with more than 100 cases, had virtually identical case counts in each supplement group (169 cases in beta-carotene group v 168 in no beta-carotene group). Neither cancer deaths (31 v 28 cases) nor total deaths (59 v 55 cases) differed by supplement group. Just 13% of women in this study were current smokers, but among these current smokers cancer counts were not different by supplement status (64 in beta-carotene group v 57 in no beta-carotene).

Retinoid Skin Cancer Prevention Actinic Keratosis Trial (SKICAP AK)

The SKICAP AK trial was one of two trials originally designed by the Southwest Skin Cancer Prevention Study Group to test retinoids in the prevention of nonmelanoma skin cancer among groups with varying degrees of risk. The SKICAP AK trial randomly assigned 2,297 adults between the ages of 21 and 84 who were considered at moderate risk by virtue of prior actinic keratoses (AKs; 10 or more) but only a limited number of prior SCCs or BCCs (no more than two permitted). Beginning in 1984, participants at clinics in Arizona were randomly assigned to daily capsules that contained either oral retinol (25,000 U daily) or placebo for up to 5 years.[14]

As reported in 1997, following an average of 3.8 years of intervention, participants who received retinol had 26% fewer SCCs than the placebo group (113 v 136 SCCs, P = .04), but there was no difference in the recurrence rate of BCCs among the 417 subjects with such outcome (P = .36).[35] The study was not designed to evaluate mortality, but while on intervention there were 22 deaths in each treatment arm. When the full follow-up period was considered (up to 61 months), there were 62 deaths in the retinol group and 53 in the placebo group (P = not significant).

LESSONS AND LEADS FROM THE FIRST GENERATION OF NUTRITIONAL INTERVENTIONS IN CANCER PREVENTION

The first generation of nutritional interventions in cancer prevention has taught us a number of invaluable lessons about designing, executing, analyzing, and interpreting large prevention trials. Perhaps most importantly, these trials have also provided us with several particularly promising leads in our efforts to prevent cancer. Beyond these lessons and leads, however, these trials have shown us the potential pitfall in over-reliance or over-interpretation of results from observational studies. Nowhere is this lesson clearer than the example of beta-carotene and lung cancer. Before completion of the randomized intervention trials

that actually tested beta-carotene supplementation in the prevention of lung cancer, nearly all the numerous published prospective observational studies showed strong associations between low dietary beta-carotene intake and/or low serum beta-carotene levels and increased lung cancer risk.[36] What a surprise then, when both the ATBC and CARET studies found that beta-carotene supplementation actually increased lung cancers. While the exact mechanisms operational here remain to be worked out, the totally unexpected results from these two trials are almost certainly real, at least in smokers. This example shows that observational epidemiology cannot be relied on alone for making health recommendations regarding vitamins and minerals and highlights the need for results from randomized clinical trials to direct public health policy in this area.

There are at least six design or operational lessons from these trials that merit comment, and these include insights regarding: (1) lag-to-effect, (2) effective duration of intervention, (3) efficacious doses, (4) use of factorial designs, (5) use of intermediate end points, and (6) toxicity.

Lag-to-Effect

With rare exception, these first generation trials largely ignored lag-to-effect considerations, or assumed that lag would be minimal (ie, 6 to 12 months). We had no empirical data to make us think otherwise, and this approach was simple and did not require planning trials of an unacceptably long duration. If we take the significant findings for both efficacy and toxicity from the first generation trials as real, we now have empirical data to use in planning similar future trials. While the benefit for selenium on total mortality and cancer incidence in the NPC study seemed to occur almost immediately, certainly by the end of the first year, effects in other trials were not discernable until much later, on the order of 18 to 48 months. The reduction in stomach cancer mortality in participants supplemented with factor D (beta-carotene plus selenium plus alpha-tocopherol) in the NIT General Population Trial, for example, appeared to start around 27 months, while the increase in lung cancer among beta-carotene (and retinol in CARET) recipients was evident by 18 months in CARET, but not until 48 months in the ATBC study. Prostate cancer risk was reduced in participants supplemented with alpha-tocopherol in the ATBC study beginning after around 18 months of intervention.

There are other important considerations regarding lag-to-effect that merit more attention than they have received to date. These include evaluation of differences in lag by age at exposure where it would be reasonable to speculate that lag might be shorter in younger individuals. We also need to consider different lags for trials that test two or more study agents and have multiple end points, often including cardiovascular events. Expected lag-to-

effect for aspirin on cardiovascular disease is shorter than lag for an antioxidant effect on a cancer outcome.

These lag-to-effect data, as well as post-trial follow-up, which permits examination of the durability of the effect (ie, the complementary "lag-to-uneffect" component of the picture), provide a unique and invaluable window on the timing, phase, and potential mechanisms of these interventions on the carcinogenesis process. Thus far, only one first generation trial, the ATBC study, has published post-trial data,[37] but the other trials are also collecting these data and updates are anticipated from them in the future. The significant findings from the ATBC study—increased lung cancer and total mortality from beta-carotene, and reduce prostate cancer from alpha-tocopherol—were further evaluated in the post-trial follow-up. An interesting symmetry of effects was noted for each of these three results; that is, the duration of effect once intervention stopped was roughly similar to the lag-to-effect time following the start of the trial (ie, approximately 4 years each for lung cancer effects, 6 years each for total mortality, and 18 months each for prostate cancer).

Effective Duration of Intervention

Deciding how long to intervene requires consideration of a number of factors, among them: (1) the underlying purpose of the study (eg, is this an initial test of an agent, or a confirmatory trial in which more detailed questions are evaluated preparatory to considering implementation of a public health supplementation or fortification plan); (2) overall study size (eg, how small an effect it is important to detect); (3) lag-to-effect and lag-to-uneffect; (4) the kinetics of test agents, including both traditional biochemical half-lives (eg, whole body half-life of selenium is 252 days,[38] so it will take several years to reach steady-state after intervention has started, or return to baseline after it has stopped) as well as biologic half-lives (eg, of enzymes influenced by the agents), with particular emphasis on kinetics within the specific target tissue of interest; and (5) logistics (eg, cost, compliance, interest of investigators). In hindsight, we now know that the cumulative incidence curves were still separating at the termination of several of these first generation trials. This suggests that the results observed underestimate maximum achievable effects, and that if we want to observe maximum effects we should design future trials to intervene longer than the typical 5 to 6 years of most of our first generation studies.

Efficacious Doses

It is axiomatic in the world of cancer therapeutics that you identify the maximum-tolerated dose, and then back off a bit. Biologic activity is linked to toxicity. While it is understandable that this same approach would be transferred to the world of cancer prevention, it is not clear that it is either necessary or desirable in prevention. The significant benefits from nutritional supplementation in the

prevention trials summarized here (and in Table 2) occurred, with the possible exception of beta-carotene, from repletion or RDA-level doses of micronutrients (ie, physiologic as opposed to pharmacologic doses). This is true for the benefits in the NIT General Population Trial for beta-carotene (20 mg) plus selenium (50 μg, just under the current dietary reference intake (DRI) value of 55 μg per day[39]) plus alpha-tocopherol (30 mg, two times the current RDA[21]) on total mortality, total cancer mortality, and stomach cancer mortality; and for retinol (5,000 U, the RDA[21]) plus zinc (22.5 mg, 1.5 times the RDA[21]) on gastric noncardia cancer mortality. It is true for the benefit in the ATBC study of alpha-tocopherol (50 mg, just over three times the current RDA) on prostate cancer. And it is essentially true for the benefit in the NPC study of selenium (200 μg, about 3.5 times the DRI) on cancer deaths, total cancer incidence, and prostate cancer. In contrast, toxicity, in the form of elevated lung cancer and total mortality in the ATBC and CARET studies, occurred only when supraphysiologic or pharmacologic doses of an especially bioavailable form of beta-carotene (20 mg) was given to otherwise well-nourished adult smokers. The ultimate setting in which the study agent is to be used must also be considered, since at- or near-physiologic doses are the appropriate choice in the setting of a public health fortification plan (eg, fortification of salt with selenium), while higher doses might be considered if individual supplementation is contemplated. Overall, the data to date support modest doses as the safest and most likely efficacious approach.

Use of Factorial Designs

Although factorial designs introduce logistical complexity, the potential for undesirable chemical and biologic interactions, and statistical complications (such as multiple comparisons), the several factorial designs employed thus far in cancer prevention trials have displayed the advantages of these designs while minimizing the problems. A total of one-half of the eight first generation trials described here used factorial designs: two studies used a 2^2 factorial (ATBC, PHS), one study used a 2^3 factorial (WHS), and one study used a one-half 2^4 fractional factorial design (NIT General Population Trial). These designs all introduced pill formulation and packaging complexities (eg, incorporation of both beta-carotene and alpha-tocopherol into a single capsule for the ATBC study; formulation of eight new and different vitamin/mineral combinations for the NIT General Population Trial). The factorial design has logistical advantages as well, perhaps most notably enhanced recruitment, because a lower percentage of the trial population is assigned to the pure placebo group (ie, only one-fourth get pure placebo in a 2^2 factorial, one-eighth in a 2^3, one-sixteenth in a 2^4, and so on). Despite logistical complexities, it appears that the major design benefits of a factorial design—the ability to test more than one hypothesis at a time and the ability to examine biologic interactions between test agents—were achieved. While this efficiency may not outweigh the problems for all intervention agents, for interventions testing vitamins and minerals, the factorial design should be the design of choice.

Use of Intermediate End Points

While the randomized, double-blind, placebo-controlled trial is the gold standard of clinical research, the "holy grail" (or platinum standard) is the use of this design in studies where actual cancer incidence or mortality is the end point (eg, phase III trials). Intermediate end points, variously and loosely defined as biomarkers or surrogates, include a wide variety of alternative end points or outcomes short of actual cancer, but hopefully highly correlated with cancer itself, and are typically part of what are termed phase II studies. While the potential promise of improved efficiency in terms of study size and duration for conducting such intermediate end point studies is enormous, to date the hope remains largely untested. The best model for validating such intermediate end points is to embed them within large randomized controlled trials, which, by design, have cancer as the primary end point. Since relatively few prevention trials with cancer end points have been conducted, there have been limited opportunities to validate such intermediate end points. The few instances in which intermediate end points have been evaluated in the context of cancer prevention trials include the comparison of intervention effects on histologic dysplasia of the esophagus,[22,40] epithelial proliferation of the esophagus,[23] premalignant cytologic abnormalities of the esophagus[24] with intervention effects on esophageal cancer as part of the NIT studies[25]; and the comparison of intervention effects on gastric premalignancy with intervention effects on stomach cancer itself within the ATBC study.[41] Results of these comparisons generally show concordance between the cancer and intermediate end point results, and offer encouragement for this potentially more efficient study approach. Interest is greatest for intermediate end points that are highly predictive of future cancers, such as esophageal squamous dysplasia.[42] Among cancer researchers there is tremendous enthusiasm and urgency for using intraepithelial neoplasias (IENs) as both prevention and treatment end points. IENs are defined as noninvasive lesions with genetic abnormalities, loss of cellular control functions, and at least some phenotypic characteristics of invasive cancer; they should also be highly predictive of invasive cancer.[43] But using IENs in cancer risk reduction studies is challenging because the multifocal and multiclonal nature of carcinogenesis makes epithelial sampling for the detection of IENs problematic, and relatively small percentages of IENs actually progress to cancer.

Toxicity

The unexpected increases in lung cancer and total mortality among participants who received beta-carotene ± retinol in the ATBC and CARET studies established a new paradigm for how we think about potential side effects from what were previously considered benign interventions. Not only must we now view all interventions as capable of both benefit and harm, but we must think beyond effects on cancer alone to monitor other major causes of morbidity and mortality.

Most Promising Prevention Leads From First Generation Trials

A summary of cancer outcomes by intervention agent and study is shown in Table 3 for the four nutritional agents most prominently evaluated in these first generation trials (ie, beta-carotene, alpha-tocopherol, selenium, and retinol). Outcomes are shown under the heading for each intervention agent whether the agent was tested individually (eg, beta-carotene in the ATBC study) or as part of a combination (eg, beta-carotene with selenium plus alpha-tocopherol in factor D in the NIT General Population Trial). Mechanistically, the anticancer effects of these nutrients have much in common and are considered to act mainly as either antioxidants (beta-carotene, alpha-tocopherol, and selenium) or differentiating agents (beta-carotene and retinol).

The nine trials summarized include 147,720 participants from disparate geographies who have widely varying exposures and very different site-specific cancer rates. As a consequence, findings tend to show substantial site and population specificity.

The most promising potential strategies for site-specific cancer prevention to emerge from these trials are: (1) alpha-tocopherol for prostate cancer (ATBC), (2) selenium for prostate cancer (NPC), (3) the combination of beta-carotene plus alpha-tocopherol plus selenium for stomach cancer (NIT General Population Trial), and (4) retinol (plus zinc) for gastric noncardia cancer (NIT General Population Trial) and squamous cell carcinoma of the skin (SKICAP AK trial).

The 32% reduction in prostate cancer with alpha-tocopherol supplementation from the ATBC study was a secondary finding based on 246 cases studied in a Western population with largely normal nutritional status but who were all smokers. No other completed trial has yet tested this hypothesis, and the prospective observational epidemiologic data supporting an association between serum alpha-tocopherol and prostate cancer are limited and weak.[44-52]

The benefit (52% reduction in prostate cancer) of selenium supplementation derives from the NPC study and is also a secondary finding, but is based on only 64 cases from a population in the southeastern United States with normal nutriture (albeit somewhat low selenium status) and a history of prior skin cancers. Although there are no other human intervention data available, the most recent prospective observational data relating selenium status to prostate cancer are consistent and strong.[47,49,53-57]

The 21% reduction in stomach cancer deaths among recipients of a beta-carotene plus alpha-tocopherol plus selenium supplement was reported based on 331 deaths in a trial conducted in rural China among peasants with poor nutritional status who have the world's highest rates of esophageal and gastric cardia cancer, and an unusual anatomic distribution of stomach cancer (approximately three-fourths occur as gastric cardia cancer and one-fourth as gastric noncardia cancer).[7] While the use of a combination supplement precluded attribution of benefit to an individual agent, subsequent analysis of baseline serum samples evaluated as part of an epidemiologic observational case-cohort study analysis in this same group indicated that the (protective) association with gastric cardia cancer was strongest for high baseline serum selenium status,[58] but protection was also suggested for persons with the highest alpha-tocopherol levels.[59] No association with serum beta-carotene levels was found.[60]

Finally, although based on just 78 cases, retinol (plus zinc) supplementation in the NIT General Population Trial reduced gastric noncardia cancer deaths by 41%. The same caveats described in the previous paragraph also apply here (same trial). Although GNCC is the anatomic site for only one-fourth of the stomach cancers in this region of China, in the rest of the world, including most of the rest of China, GNCC is by far the most common location for stomach cancer. In a separate trial conducted in the United States among people at moderate risk of recurrent skin cancer (they had a prior history of actinic keratosis and skin cancer), retinol (alone) reduced squamous cell carcinoma of the skin.[35]

For both the stomach cancer and GNCC results from the NIT General Population Trial, we also have similar trial data from the ATBC study. In the ATBC study, based on 126 total stomach cancer cases (including 98 GNCC), no benefit for either alpha-tocopherol or beta-carotene was seen for either stomach cancer in toto or GNCC alone.[29]

In addition to the statistically significant findings from this first generation of trials noted above, there are several other insignificant but suggestive intervention-based leads worth watching as potential study agents in future trials. These include selenium and alpha-tocopherol in the prevention of lung and colorectal cancer prevention. For lung cancer, there was a suggested trend for reduced incidence in the later years for alpha-tocopherol in the ATBC study,[8] a reduced rate of lung cancer in the NPC study for selenium,[33] and, though based on just 31 lung cancer deaths, a hint of reduction in the NIT General Population Trial for participants who received factor D

Table 3. Summary of Outcomes as Relative Risks by Intervention Agent and Study

Outcome	Intervention Agent			
	Beta-Carotene	Alpha-Tocopherol	Selenium	Retinol
Mortality				
Total	1.10 (SCPS)	0.93 (NIT DT)	0.93 (NIT DT)	0.93 (NIT DT)
	0.93 (NIT DT)	0.91* (NIT GPT)	0.91* (NIT GPT)	1.00 (NIT GPT)
	0.91* (NIT GPT)	1.02 (ATBC)	0.79 (NPC)	1.17* (CARET)
	1.08* (ATBC)			1.00 (SKICAP AK)
	1.01 (PHS)			
	1.17* (CARET)			
	1.11 (WHS)			
Cancer	0.96 (NIT DT)	0.96 (NIT DT)	0.96 (NIT DT)	0.96 (NIT DT)
	0.87* (NIT GPT)	0.87* (NIT GPT)	0.87* (NIT GPT)	0.97 (NIT GPT)
	1.02 (PHS)		0.59* (NPC)	
Esophageal/gastric cardia	0.92 (NIT DT)	0.92 (NIT DT)	0.92 (NIT DT)	0.92 (NIT DT)
	0.90 (NIT GPT)	0.90 (NIT GPT)	0.90 (NIT GPT)	1.04 (NIT GPT)
Esophageal	0.84 (NIT DT)	0.84 (NIT DT)	0.84 (NIT DT)	0.84 (NIT DT)
	0.96 (NIT GPT)	0.96 (NIT GPT)	0.96 (NIT GPT)	0.93 (NIT GPT)
Stomach	1.18 (NIT DT)	1.18 (NIT DT)	1.18 (NIT DT)	1.18 (NIT DT)
	0.79* (NIT GPT)	0.79* (NIT GPT)	0.79* (NIT GPT)	1.03 (NIT GPT)
Gastric cardia	1.04 (NIT DT)	1.04 (NIT DT)	1.04 (NIT DT)	1.04 (NIT DT)
	0.82 (NIT GPT)	0.82 (NIT GPT)	0.82 (NIT GPT)	1.22 (NIT DT)
Gastric noncardia	2.68 (NIT DT)	2.68 (NIT DT)	2.68 (NIT DT)	2.8 (NIT DT)
	0.72 (NIT GPT)	0.72 (NIT GPT)	0.72 (NIT GPT)	0.59* (NIT GPT)
Cancer incidence				
Total	1.01 (NIT DT)	1.01 (NIT DT)	1.01 (NIT DT)	1.01 (NIT DT)
	0.93 (NIT GPT)	0.93 (NIT GPT)	0.93 (NIT GPT)	1.00 (NIT GPT)
	0.98 (PHS)		0.75* (NPC)	
	1.03 (WHS)			
Nonmelanoma skin	1.05 (SCPS)		1.17* (NPC)	
Basal cell skin	1.04 (SCPS)		1.09 (NPC)	1.06 (SKICAP AK)
Squamous cell skin	1.22 (SCPS)		1.25* (NPC)	0.74* (SKICAP AK)
Melanoma	0.88 (PHS)			
Lung	1.16* (ATBC)	0.99 (ATBC)	0.74 (NPC)	1.28* (CARET)
	0.93 (PHS)			
	1.28* (CARET)			
Prostate	1.23 (ATBC)	0.68* (ATBC)	0.48* (NPC)	
	0.99 (PHS)			
Urothelial	1.0 (ATBC)	1.1 (ATBC)		
Kidney	0.8 (ATBC)	1.1 (ATBC)		
Stomach	1.17 (NIT DT)	1.17 (NIT DT)	1.17 (NIT DT)	1.17 (NIT DT)
	0.84* (NIT GPT)	0.84* (NIT GPT)	0.84* (NIT GPT)	0.96 (NIT GPT)
	1.26 (ATBC)	1.21 (ATBC)		
Gastric cardia	1.05 (NIT DT)	1.05 (NIT DT)	1.05 (NIT DT)	1.05 (NIT DT)
	0.85 (NIT GPT)	0.85 (NIT GPT)	0.85 (NIT GPT)	1.02 (NIT GPT)
	1.81 (ATBC)	1.00 (ATBC)		
Gastric noncardia	3.54* (NIT DT)	3.54* (NIT DT)	3.54* (NIT DT)	3.54* (NIT DT)
	0.82 (NIT GPT)	0.82 (NIT GPT)	0.82 (NIT GPT)	0.73 (NIT GPT)
	1.13 (ATBC)	1.27 (ATBC)		
Colorectal	1.05 (ATBC)	0.78 (ATBC)	0.46 (NPC)	
	0.96 (PHS)			
Breast	1.01 (WHS)			
Lymphoma	1.08 (PHS)			

Abbreviations: SCPS, Skin Cancer Prevention Study[5]; NIT, Nutrition Intervention Trial; DT, Dysplasia Trial[6]; GPT, General Population Trial[7]; ATBC, Alpha-Tocopherol Beta-Carotene study[8]; NPC, Nutritional Prevention of Cancer study[12]; PHS, Physicians' Health Study[9]; CARET, Beta-Carotene and Retinol Efficacy Trial[10]; WHS, Women's Health Study[13]; SKICAP AK, Retinoid Skin Cancer Prevention Actinic Keratosis Trial.[14]
*P value is statistically significant (P < .05).

(beta-carotene + selenium + alpha-tocopherol).[61] For colorectal cancer, insignificant but reduced rates were noted in the ATBC study for alpha-tocopherol,[27] and similar results were seen in the NPC study for selenium.[12]

Other lines of evidence in humans, other than from phase III trials (eg, observational epidemiologic studies, phase IIB trials with premalignant lesions such as colorectal polyps as end points), have also produced promising prevention leads for other nutritional study agents. Perhaps most noteworthy among these are calcium,[62] vitamin D, and folate in colorectal cancer prevention (reviewed in Lamprecht et al[63]), and lycopene for the prevention of prostate cancer (reviewed in Giovannucci[64,65]).

FUTURE PROSPECTS

A number of other phase III trials using nutritional study agents have been initiated since the first generation trials were started, and the results of these efforts will be available over the next several years. These second generation

trials include the Women's Health Initiative clinical trials (testing calcium plus vitamin D for hip fracture as the main end point, and other fractures and colorectal cancer as secondary end points),[66] PHS II (testing beta-carotene, alpha-tocopherol, ascorbic acid, and/or daily multivitamins in the prevention of cancer, cardiovascular, and eye diseases),[67] the Supplementation en Vitamins et Mineraux Antioxydants (SU.VI.MAX study; testing the combination of ascorbic acid plus alpha-tocopherol plus beta-carotene plus selenium plus zinc in the prevention of all-site cancers and ischemic heart diseases),[68] the Selenium and Vitamin E Cancer Trial (SELECT; testing selenium and/or alpha-tocopherol in the prevention of prostate cancer),[69] as well as the alpha-tocopherol arm of the WHS, which continued after beta-carotene was stopped.[13]

Phase III cancer prevention trials using bioactive food constituents as the study agent have thus far had the following as their primary rationale: a convergence of epidemiologic research results; an intriguing secondary end point in a phase III trial done for another purpose; or laboratory evidence including largely empirical results showing cancer prevention in animal models. It is likely that in the future, the rationale will necessarily include phase II clinical trial results showing biologic activity suggestive of a benefit in humans and mechanistic evidence based upon modern basic science approaches to biomedical research.

Biomarker research is necessary to inform nutritional intervention trials, but needs to be greatly augmented in specific areas that are bottlenecks to the advancement of nutritional science. For example, greater emphasis is needed on the development and use of clinical laboratory markers of dietary intake, which then must be incorporated into epidemiologic studies in order to complement the rather crude questionnaire data that are considered state-of-the-art today.

In addition to the complications introduced by the potential impact of age, time-of-life, duration, and level of exposure, intervention trials have a practical maximum duration of intervention of 5 to 10 years. Thus, there must be evidence that an intervention of that duration might be effective.

Exfoliated cells or biopsy tissue can be used to establish that the intervention agent reaches the target tissue in an appropriate concentration, and further molecular studies can be done regarding mechanisms of action in that tissue. It is known that serum and blood cells may not accurately reflect target tissue levels. Exfoliated cells can readily be obtained from the buccal mucosa,

sputum, stool, urine, and nipple aspirates, and there is evidence that dietary components can modify molecular markers in these cells. Presurgical chemopreventive interventions are another important way to study tissue levels and function within the target organ. This has been particularly useful in the preprostatectomy model. An intervention of several weeks is sufficient for the agent to get to the gland. Careful sectioning allows study of the different areas and different types of cells within the gland.

Bioactive food components may be protective at different stages in the carcinogenesis process. Thus, pathologic or biomarker evidence of the stage of precancer can be extremely useful for defining eligibility criteria for participants. Diagnosis of precancer and stage of carcinogenesis also may be used as end points in phase II trials. This dictates that investigators give careful attention to criteria for diagnosis, criteria for progression, and anatomic location of the lesion.

There are already more exciting leads of how bioactive food components may reduce cancer risk than there are practical possibilities for phase III trials. Consequently, prioritization strategies and efficiency of clinical trial design are major considerations in planning for future phase III prevention trials. The case for equipoise of the study hypothesis should be convincing. Factorial designs often should be used, and the possibility of multiple primary end points, including end points crossing disease categories, should be envisioned.

When phase III cancer prevention trials of food constituents are launched, these should be augmented with biorepositories, intensive associated basic nutritional science studies, attempts to validate potential future surrogate end point biomarkers, and consideration of long-term follow-up after the trial ends to document late beneficial or adverse effects. The overwhelming evidence of a major role of nutrition in carcinogenesis, the many leads that nutritional intervention may reduce cancer incidence, and the growth and increasing sophistication of our clinical trials networks points to a very promising future for nutritional intervention trials leading to substantial public benefit.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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